REMARKS

Claims 113-119 are pending. Claim 114 has been canceled without prejudice to pursue the subject matters in a future continuation application and the corresponding subject matter incorporated into claim 113. Claim 118 is withdrawn and new claims 120-125 are added. No claim amendment adds new matter. Accordingly, applicants respectfully request the entry of this Amendment. Upon entry, claims 113, 115 to 125 are pending and under examination.

Examiner's comments are addressed in sequence below. During the entire course of the prosecution of this application, Applicants have articulated several bases for withdrawing the prior art rejection and have supplied evidence to support these positions. Although the ensuing remarks are believed sufficient to overcome all rejections, Applicants retain the intent and the right to rely on all previous positions for the purpose of appeal.

Rejections Under § 112

1. The rejection of claim 114 is mooted in view of the amendments cancelling claim 114 and incorporating it into claim 113.

It is respectfully requested that this rejection be withdrawn.

2. Claims 113, 115-117 and 119 are rejected for not adequately being described in the specification and for not being enabled

by the disclosure therein. Claim 113 has been amended to recite that the tumor-targeted bacteria is a Salmonella msbB$^-$ mutant.

Although not in agreement with the rejection, Applicants respectfully submit that the foregoing amendment of claim 113 overcomes these rejections.

Rejection Over the Combination of Low in view of Schachter

Examiner's comments are responded to below:

1. The Prior Art Does Not Teach Every Claim Limitation

Examiner states:

Applicants go on to argue that the Office has not provided a single piece of evidence that tumor-targeted bacteria are art-recognized equivalents of IFN-a and or GM-CSF. Applicants also argue that there is no suggestion to specifically combine the cisplatin with the tumor-targeted bacteria.

In response, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Response:

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. MPEP § 2143.03. (Emphasis added). It is respectfully submitted that Examiner has yet to specifically articulate how each and every claim limitation is taught or suggested as required. MPEP § 706.02(j), Contents of a 35 U.S.C. 103 Rejection (indicating that a response must include showing

"(C)the proposed modification of the applied reference(s) necessary to arrive at the claimed subject matter,…). This has not yet been supplied by the rejection.

Examiner argues that the issue is not whether claimed invention is expressly suggested in any one or all of the references. This is irrelevant to the issue in Applicants' comments. The issue is that there has not been a specific line of legal reasoning that bridges Low's modification by Schachter to arrive at the specific claim limitations. In other words, the disclosure by the references need not be explicit, but Examiner's explanation must be. For example, Examiner states that she does not suggest that attenuated tumor-targeted Salmonella and cytokines are interchangeable equivalents. Yet this must be in part what is behind her rationale. If not, how does Examiner get from Low/Schachter to the specific claim limitations.

Examiner has adopted a generalized approach in issuing this rejection that ignores the core requirement of explaining how the combined references teach or suggest each limitation in the rejected claims. It is incumbent upon the Examiner to explain how persons of ordinary skill in the art would actually know to combine these references to arrive at the method comprising of each recited limitation with a reasonable expectation of success. MPEP § 706.02(j), Contents of a 35 U.S.C. 103 Rejection.

According to Examiner's comments, the attenuated tumor-targeted Salmonella and cytokines are not art-recognized equivalents. Nor do the references specifically have to suggest combining only cisplatin with attenuated tumor-targeted Salmonella. Then how do the references suggest the specific combination of the limitations in the rejected claims?

In the course of this prosecution the specific modifications required to establish a *prima facie* case under 103(a)(a) has not yet been appeared in the record. It is respectfully submitted that this is because the gaps between the teachings of Low and Schachter are far too great to arrive at the specific claim

limitations. In other words, the required nexus cannot be put on the record because it cannot be properly formulated according to longstanding PTO guidelines relating to 103(a).

Accordingly, the rejection under § 103(a) is improper and should be withdrawn.

2. The Rationale Supporting the Rejection is "Obvious to Try" and no More

Examiner states:

Schachter et al., further supplemented Low et al., by illustrating it was within the level of the skilled to combine a routine chemotherapeutic regimen with a newly developed biotherapy in treating solid tumors such as melanoma.

…the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Here, the Office does not suggest that the attenuated bacteria is an equivalent of cytokines use by Schachter et al, rather, *Schachter at al is relied on for a general desirability of combining a new therapeutic regimen with an existing conventional one*. In a clinical setting, the skilled rarely uses only one drug/one type of therapy in a cancer therapeutic regimen, *combining a chemotherapy with radiotherapy or newly developed cytokine, bacteria, gene therapy is often the routine*.

Response:

As the Federal Circuit said *In re Farrell*, "[o]bvious to try" has long been held not to constitute obviousness. *A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be* carried out. *In re O'Farrell*, 7 USPQ2d 1673, 1680-81 (Fed.Cir.1988)).

It is respectfully submitted that *Farrell* precisely describes the nature of the rationale underlying the instant rejection. In

Examiner's own words, Schachter is relied on *for a general desirability* to try new combinations of anti-cancer agents.

The fact that the skilled clinician "rarely uses only one drug/one type of therapy" is wholly irrelevant to the claims. Examiner states in only a general manner that combining a chemotherapy with radiotherapy or newly developed cytokines, bacteria, gene therapy is often the routine. This statement only further establishes the general nature of Examiner's relying on Schacter to find ways to treat cancer by combining entirely different fields of therapy.

The rejection is based on a general invitation to experiment which is classic "obvious to try" reasoning. Respectfully, the rejection is improper and should be withdrawn.

3. Examiner's Proposed Modification Both (a) Alters the Principle Underlying Schachter's Therapy and (b) Would Render it Unsatisfactory For its Intended Purpose

Examiner states:

Schachter et al supplemented Low et al by disclosing a routine regimen of chemotherapy comprising cisplatin (a chemotherapeutic agent) for treating human melanoma, and establishing that it was well known in the art [sic]a combined drug therapy had been clinical routine since one single drug was insufficient for combating cancer.

In a clinical setting, the skilled [sic] rarely uses only one drug/one type of therapy in a cancer therapeutic regimen, combining a chemotherapy with radiotherapy or newly developed cytokine, bacteria, gene therapy is often the routine.

Response:

(a) According to established examination guidelines, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not

sufficient to render the claims prima facie obvious. MPEP § 2143.01,VI, citing, In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)(Emphasis added).

The second paragraph from the office action cited above indicates that the instant rejection results from, *inter alia*, not considering the underlying principles of various broad categories of cancer therapies, e.g., "combining a chemotherapy with radiotherapy or newly developed cytokine, bacteria, gene therapy is often routine." Whether or not this assessment of the art is even accurate, what is clear from patent law perspective is that it is not a proper line of reasoning to establish a *prima facie* case of obviousness. MPEP § 2143.01,VI.

This disregard for underlying principles applies to the instant rejection. Schachter's method is based on priming and immunomodulating the immune system before and after the chemotherapy, respectively. See Schachter, p. 156, col 1, and p. 157 col. 1. Schachter notes that IL-2 had been shown to somewhat effective in combination with IFN-alpha but was "hampered by severe toxicity." Schachter, p. 156, top col. 2. What is clear is that Schachter seeks to boost the immune system that is likely to be damaged by chemotherapy, and avoid further toxicity and/or immune challenges.

In order for the instant rejection to be proper, *inter alia*, the attenuated tumor-targeted Salmonella would have to substitute for the cytokines as Schachter's immune primer and modulator. There is no evidence of this practice or any supporting hypothesis. There is no evidence that attenuated tumor-targeted Salmonella provide anti-tumor effects that are based on boosting the immune system.

In sum, there is no basis to conclude that persons of ordinary skill in the art believe that attenuated tumor-targeted Salmonella work by a similar principle as do cytokines. In addition, Examiner has asserted that she does not consider Schachter's cytokines as equivalents to attenuated tumor-

targeted Salmonella. Therefore, in Examiner's own words, the proposed modification of Low with Schachter's methodology would dramatically alter the principle underlying Schachter's method.

It is respectfully suggested that the instant rejection be withdrawn.

(b) In addition, if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. MPEP § 2143.01,V, citing, *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984) (Emphasis added).

Examiner asserts that Schachter's combined cytokine-chemotherapy regimen "establishes" that combined therapy is since one single drug is insufficient. It must follow that any modification of Schachter that suggests using only one of the four drugs in his chemotherapy regimen would, in Examiner's words, be insufficient. The unavoidable conclusion here is that Examiner's proposed modification of using only cisplatin and omitting the additional three drugs, would render Schachter's method unsuitable (i.e., insufficient) for his intended purpose. This violates the rule of *In re Gordon* and MPEP § 2143.01,V.

Further, against this background, it is indisputable that Applicants have proceeded contrary to accepted wisdom by eliminating three chemotherapy agents. This has long been held to be strong evidence of nonobviousness. MPEP § 2145.

On this basis, it is respectfully suggested that the rejection be withdrawn.

4. The Claimed Invention May Be Compared With Prior Art That Is Closer Than That Applied By Examiner - MPEP 716.02(e)

Examiner States:

The applicant argues that they have shown a synergism between attenuated Salmonella and Cisplatin or cytoxan, which cannot be predicted by the combined teachings in view of the results of mitomycin C in figure 39.

In response, it is noted mitomycin C alone does not have much of an efect [sic] compared to the control, and thus, one would not expect this would change when combined with the Salmonella. As to the synergistic efect [sic], it was achieved by a particular drug with a particular strain of Salmonella, thus the scope of the claims should limited to the bacteria strain. The court has determined, "whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." IN OTHER WORDS, THE SHOWING OF UNEXPECTED RESULTS MUST BE REVIEWED TO SEE IF THE RESULTS OCCUR OVER THE ENTIRE CLAIMED RANGE.

Response:

As set forth in MPEP § 716.02(e) "Applicants may compare the claimed invention with prior art that is more closely related to the invention than the prior art relied upon by the examiner." In re Holladay, 584 F.2d 384, 199 USPQ 516 (CCPA 1978); Ex parte Humber, 217 USPQ 265 (Bd. App. 1961).

It must first be clarified that although a synergism was demonstrable between attenuated tumor-targeted Salmonella and cytoxan or cisplatin, it does not necessarily follow that Applicants are arguing "unexpected and superior results." Applicants are merely drawing attention to their data in figures 39-41 to illustrate that there exist in the art some degree of unpredictability when comparing the efficacy of attenuated tumor-targeted Salmonella alone or in combination with one of either mitomycin (NO effect) to that of cisplatin and cytoxan. This comparison is scientifically far closer and more relevant than the generalized motivation Examiner extracts from the

combined disclosures of Low and Schachter. Further, such comparisons are explicitly authorized pursuant to MPEP § 716.02(e).

The data illustrated in Figure 39 demonstrate that administering mitomycin alone provided little, if any, improvement over the control saline in restricting tumor size. The same effect was demonstrated with cisplatin or cytoxan when individually administered in the absence of attenuated tumor-targeted Salmonella. Importantly, the mitomycin did not augment the effect of attenuated tumor-targeted Salmonella.

When cisplatin was administered on its own a demonstrable but modest restriction of tumor size was seen in comparison to the saline control (See Figure 41). However, when cisplatin was combined with attenuated tumor-targeted Salmonella, the magnitude of reduction in tumor size was substantially greater than with either cisplatin alone at 29 days, or with attenuated tumor-targeted Salmonella alone at 40 days.

These results indicate that there is a degree of unpredictability in the art that precludes having a reasonable expectation of success in substituting one therapeutic agent.

If one considers the steps required to modify Low in view of Schachter, the number of unpredictable modifications of Low/Schachter that would be necessary to arrive at the claimed method cannot reasonably be expected to provide any success in achieving the claimed method.

For this reason, combining Low and Schachter cannot have provided the reasonable expectation of success required to establish a prima facie case under § 103(a). Accordingly the rejection should be withdrawn.

CONCLUSION

It is respectfully suggested that in view of the amendments to the claims and the foregoing remarks that the application is in condition for allowance and that allowance is respectfully requested.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,

Albert Wai-Kit Chan

Albert Wai-Kit Chan
Registration No. 36,479
Attorney for Applicant(s)
Law Offices of
Albert Wai-Kit Chan, PLLC
World Plaza, Suite 604
141-07 20th Avenue
Whitestone, New York 11357
Tel: (718) 799-1000
Fax: (718) 357-8615
E-mail: chank@kitchanlaw.com